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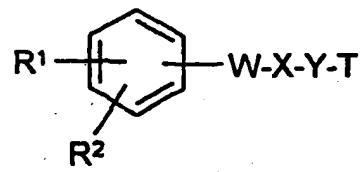
(54) Title: PHENYL DERIVATIVES AND THEIR USE IN THE TREATMENT OF THROMBOEMBOLIC DISORDERS OR TUMOURS

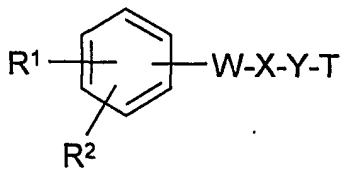


(I)

(57) Abstract: Compounds of the formula (I) in which R^1 is CN, or $C(=NH)-NH_2$, $CON(R^3)_2$ or $[C(R^4)_2]_nN(R^3)_2$, each of which is unsubstituted or monosubstituted by $C(=O)R^3$, $COOR^3$, or^3 or by a conventional amino-protecting group, or W is $-NR^3CO-$, $-NR^3COC(R^4)_2$, $NR^3C(R^4)¿2)$ or $-C(R^4)_2NR^3C(R^4)_2-$, X is $-C(R^3)_2-$, $-[C(R^3)_2]_2-$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^3$, Y is alkylene, cycloalkylene, Het-diyl or Ar-diyl, T is OR^3, $N(R^3)_2$, $N(R^3)_2CON(R^3)_2$, a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/sor S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted, or a phenyl radical which is unsubstituted or monosubstituted, disubstituted or trisubstituted are inhibitors of coagulation factor Xa and can be employed for the prophylaxis and/or therapy of thromboembolic disorders and for the treatment of tumours.

PHENYL DERIVATIVES AND THEIR USE IN THE TREATMENT OF THROMBOEMBOLIC DISORDERS OR TUMOURS

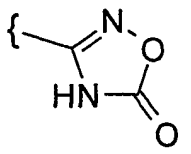
The invention relates to compounds of the formula I



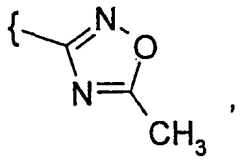
I

in which

R^1 is CN, or $-C(=NH)-NH_2$, $CON(R^3)_2$ or $-[C(R^4)_2]_nN(R^3)_2$, each of which is unsubstituted or monosubstituted by $C(=O)R^3$, $COOR^3$, OR^3 or by a conventional amino-protecting group, or



or



,

R^2 is H, Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, $-[C(R^4)_2]_n$-Ar, $-[C(R^4)_2]_n$-Het or $-[C(R^4)_2]_n$-cycloalkyl,

R^3 is H, A, $-[C(R^4)_2]_n$-Ar, $-[C(R^4)_2]_n$-Het or $-[C(R^4)_2]_n$-cycloalkyl,

R^4 is H or A,

W is $-NR^3CO-$, $-NR^3COC(R^4)_2$, $NR^3C(R^4)_2$ or $-C(R^4)_2NR^3C(R^4)_2-$,

X is $-C(R^3)_2-$, $-[C(R^3)_2]_2-$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^3$,

Y is alkylene, cycloalkylene, Het-diyl or Ar-diyl,

T is OR^3, $N(R^3)_2$, $N(R^3)_2CON(R^3)_2$,

a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, $-[C(R^4)_2]_n$-Ar, $-[C(R^4)_2]_n$-Het, $-[C(R^4)_2]_n$-cycloalkyl, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, $S(O)_mA$ and/or carbonyl oxygen, or

a phenyl radical which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, -[C(R^4)$_2$]$_n$-Ar, -[C(R^4)$_2$]$_n$-Het, -[C(R^4)$_2$]$_n$-cycloalkyl, OR^3, N(R^3)$_2$, NO_2, CN, $COOR^3$, CON(R^3)$_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3 or S(O)$_m$A,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by -CH=CH- groups and/or, in addition, 1-7 H atoms may be replaced by F,

Ar is phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^4, N(R^4)$_2$, $NR^4CON(R^4)_2$, NO_2, CN, $COOR^4$, CON(R^4)$_2$, NR^4COA, NR^4SO_2A, COR^4, SO_2NR^4 or S(O)$_m$A,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, -[C(R^4)$_2$]$_n$-Ar, -[C(R^4)$_2$]$_n$-Het', -[C(R^4)$_2$]$_n$-cycloalkyl, OR^3, N(R^3)$_2$, $NR^4CON(R^4)_2$, NO_2, CN, $COOR^3$, CON(R^3)$_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, S(O)$_m$A and/or carbonyl oxygen,

Het' is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or disubstituted by Hal, A, OR^3, N(R^3)$_2$, NO_2, CN, $COOR^3$, CON(R^3)$_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, S(O)$_m$A and/or carbonyl oxygen,

Hal is F, Cl, Br or I,

m and n are each, independently of one another, 0, 1 or 2,

and their pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios.

The invention had the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties and are well tolerated. In particular, they exhibit factor Xa-inhibiting properties and can therefore be employed for combating and preventing thromboembolic disorders, such as thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexia, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

The compounds of the formula I according to the invention may furthermore be inhibitors of the coagulation factors factor VIIa, factor IXa and thrombin in the blood coagulation cascade.

Aromatic amidine derivatives having an antithrombotic action are disclosed, for example, in EP 0 540 051 B1, WO 00/71508, WO 00/71511, WO 00/71493, WO 00/71507, WO 00/71509, WO 00/71512, WO 00/71515 and WO 00/71516. Cyclic guanidines for the treatment of thromboembolic disorders are described, for example, in WO 97/08165. Aromatic heterocyclic compounds having factor Xa-inhibitory activity are disclosed, for example, in WO 96/10022. Substituted N-[(aminoiminomethyl)phenylalkyl]azaheterocyclylamides as factor Xa inhibitors are described in WO 96/40679.

The antithrombotic and anticoagulant effect of the compounds according to the invention is attributed to the inhibitory action against activated coagulation protease, known by the name factor Xa, or to the inhibition of other activated serine proteases, such as factor VIIa, factor IXa or thrombin.

Factor Xa is one of the proteases involved in the complex process of blood coagulation. Factor Xa catalyses the conversion of prothrombin into thrombin. Thrombin cleaves fibrinogen into fibrin monomers, which, after crosslinking, make an elementary contribution to thrombus formation.

Activation of thrombin may result in the occurrence of thromboembolic disorders. However, inhibition of thrombin may inhibit the fibrin formation involved in thrombus formation.

The inhibition of thrombin can be measured, for example, by the method of G.F. Cousins et al. in *Circulation* **1996**, *94*, 1705-1712.

Inhibition of factor Xa can thus prevent the formation of thrombin.

The compounds of the formula I according to the invention and their salts engage in the blood coagulation process by inhibiting factor Xa and thus inhibit the formation of thrombuses.

The inhibition of factor Xa by the compounds according to the invention and the measurement of the anticoagulant and antithrombotic activity can be determined by conventional in-vitro or in-vivo methods. A suitable method is described, for example, by J. Hauptmann et al. in *Thrombosis and Haemostasis* **1990**, *63*, 220-223.

The inhibition of factor Xa can be measured, for example, by the method of T. Hara et al. in *Thromb. Haemostas.* **1994**, *71*, 314-319.

Coagulation factor VIIa initiates the extrinsic part of the coagulation cascade after binding to tissue factor and contributes to the activation of factor X to give factor Xa. Inhibition of factor VIIa thus prevents the formation of factor Xa and thus subsequent thrombin formation.

The inhibition of factor VIIa by the compounds according to the invention and the measurement of the anticoagulant and antithrombotic activity can be determined by conventional in-vitro or in-vivo methods. A conventional method for the measurement of the inhibition of factor VIIa is described, for example, by H. F. Ronning et al. in *Thrombosis Research* **1996**, *84*, 73–81.

Coagulation factor IXa is generated in the intrinsic coagulation cascade and is likewise involved in the activation of factor X to give factor Xa. Inhibition of factor IXa can therefore prevent the formation of factor Xa in a different way.

The inhibition of factor IXa by the compounds according to the invention and the measurement of the anticoagulant and antithrombotic activity can be determined by conventional in-vitro or in-vivo methods. A suitable method is described, for example, by J. Chang et al. in *Journal of Biological Chemistry* **1998**, *273*, 12089-12094.

The compounds according to the invention may furthermore be used for the treatment of tumours, tumour illnesses and/or tumour metastases. A correlation between tissue factor TF / factor VIIa and the development of various types of cancer has been indicated by T.Taniguchi and N.R. Lemoine in Biomed. Health Res. (2000), 41 (Molecular Pathogenesis of Pancreatic Cancer), 57-59.

The publications listed below describe an antitumoural action of TF-VII and factor Xa inhibitors for various types of tumour:

K.M. Donnelly et al. in Thromb. Haemost. 1998; 79: 1041-1047;

E.G. Fischer et al. in J. Clin. Invest. 104: 1213-1221 (1999);

B.M. Mueller et al. in J. Clin. Invest. 101: 1372-1378 (1998);

M.E. Bromberg et al. in Thromb. Haemost. 1999; 82: 88-92

The compounds of the formula I can be employed as medicament active ingredients in human and veterinary medicine, in particular for the treatment and prevention of thromboembolic disorders, such as thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexia, angina pectoris, restenosis after angioplasty, claudicatio intermittens, venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, unstable angina and strokes based on thrombosis.

The compounds according to the invention are also employed for the treatment or prophylaxis of atherosclerotic diseases, such as coronary arterial disease, cerebral arterial disease or peripheral arterial disease.

The compounds are also employed in combination with other thrombolytic agents in the case of myocardial infarction, furthermore for prophylaxis for reocclusion after thrombolysis, percutaneous transluminal angioplasty (PTCA) and coronary bypass operations.

The compounds according to the invention are furthermore used for the prevention of rethrombosis in microsurgery, furthermore as anticoagulants in connection with artificial organs or in haemodialysis.

The compounds are furthermore used in the cleaning of catheters and medical aids *in vivo* in patients, or as anticoagulants for the preservation of blood, plasma and other blood products *in vitro*. The compounds according to the invention are furthermore used for illnesses in which blood coagulation makes a crucial contribution to the course of the illness or represents a source of secondary pathology, such as, for example, in cancer, including metastasis, inflammatory disorders, including arthritis, and diabetes.

In the treatment of the illnesses described, the compounds according to the invention are also employed in combination with other thrombolytically active compounds, such as, for example, with "tissue plasminogen activator" t-PA, modified t-PA, streptokinase or urokinase. The compounds according to the invention are given either at the same time as or before or after the other substances mentioned.

Particular preference is given to simultaneous administration with aspirin in order to prevent recurrence of the clot formation.

The compounds according to the invention are also used in combination with blood platelet glycoprotein receptor (IIb/IIIa) antagonists, which inhibit blood platelet aggregation.

The invention relates to the compounds of the formula I and their salts and to a process for the preparation of compounds of the formula I according to Claim 1 and their salts, characterised in that

a) they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent by

i) liberating an amidino group from their hydroxyl, oxadiazole or oxazolidinone derivative by hydrogenolysis or solvolysis,

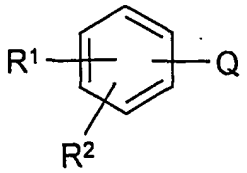
ii) replacing a conventional amino-protecting group by hydrogen by treatment with a solvolysing or hydrogenolysing agent, or liberating an amino group protected by a conventional protecting group,

or

b) a cyano group is converted into an N-hydroxyamidino group,

or

c) a compound of the formula II

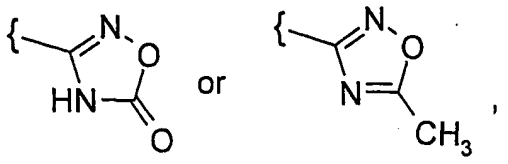


II

in which

Q is HNR^3- or $C(R^4)_2NHR^3$,

R^1 is $-C(=NH)-NH_2$ which is monosubstituted by $C(=O)R^3$, $COOR^3$, OR^3 or by a conventional amino-protecting group, or is



and R^2, R^3 and R^4 are as defined in Claim 1, with the proviso that, if R^2 contains a free amino group, this in protected form,

is reacted with a compound of the formula III

III

$$Z\text{-}X\text{-}Y\text{-}T \qquad III$$

in which

Z is -CO-L, $-C(R^4)_2$-CO-L or $-C(R^4)_2$-L,

L is Cl, Br, I or a free or reactively functionally modified OH group, and

X, Y and T are as defined in Claim 1, with the proviso that, if T is or contains a free amino group, this in protected form,

and/or

d) a base or acid of the formula I is converted into one of its salts.

The invention also relates to the optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers and the hydrates and solvates of these compounds. The term solvates of the compounds is taken to mean adductions of inert solvent molecules onto the compounds which form owing to their mutual attractive force. Solvates are, for example, monohydrates or dihydrates or alcoholates.

The term pharmaceutically usable derivatives is taken to mean, for example, the salts of the compounds according to the invention and also so-called prodrug compounds.

The term prodrug derivatives is taken to mean compounds of the formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the organism to give the effective compounds according to the invention.

These also include biodegradable polymer derivatives of the compounds according to the invention, as described, for example, in Int. J. Pharm. 115, 61-67 (1995).

The invention also relates to mixtures of the compounds of the formula I according to the invention, for example mixtures of two diastereomers, for example in the ratio 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 or 1:1000.

These are particularly preferably mixtures of stereoisomeric compounds.

The invention also relates, in particular, to the -C(=NH)-NH_2- compounds of the formula I which are substituted by -COA, -COOA, -OH or by a conventional amino-protecting group.

For all radicals which occur more than once, such as, for example, A, their meanings are independent of one another.

Above and below, the radicals or parameters W, X, Y, T, R^1 and R^2 are as defined under the formula I, unless expressly stated otherwise.

A is alkyl, is unbranched (linear) or branched, and has 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. A is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1- , 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1- , 2- , 3- or 4-methylpentyl, 1,1- , 1,2- , 1,3- , 2,2- , 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, furthermore preferably, for example, trifluoromethyl.

A is very particularly preferably alkyl having 1-6 carbon atoms, preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl or trifluoromethyl.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

Alkylene is preferably methylene, ethylene, propylene, butylene, pentylene or hexylene, furthermore branched alkylene.

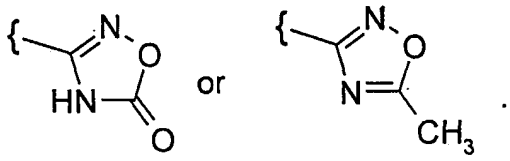
$-COR^3$ (acyl) is preferably formyl, acetyl, propionyl, furthermore also butyryl, pentanoyl, hexanoyl or, for example, benzoyl.

Ph is phenyl, Me is methyl, Et is ethyl, BOC is tert-butoxycarbonyl.

Hal is preferably F, Cl or Br, but alternatively I.

If R^1 is $CON(R^3)_2$ or $-[C(R^4)_2]_nN(R^3)_2$, $CONH_2$, NH_2 or CH_2NH_2 is preferred.

R^1 is particularly preferably CN, NH_2, CH_2NH_2, $CH_2CH_2NH_2$, $-C(=NH)-NH_2$ which is unsubstituted or monosubstituted by OH, or is



R^2 is preferably H.

R^3 is preferably H, A or $-(CH_2)_n$-Ar, particularly preferably, for example, H, alkyl having 1-6 carbon atoms, phenyl or benzyl.

X is preferably $-CHR^3$, $-CHR^3-O-$, where R^3 is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms, phenyl or benzyl

W is preferably NHCO, $NHCOCH_2$, $NHCH_2$ or CH_2NHCH_2, very particularly preferably NHCO.

Y is preferably alkylene or Ar-diyl, particularly preferably methylene, ethylene, propylene, or 1,4-phenylene which is unsubstituted or mono-substituted by F, ethoxycarbonylmethoxy or carboxymethoxy, furthermore alternatively pyridinedyl, preferably pyridine-2,5-diyl. Y is in particular 1,3- or 1,4-phenylene.

T is preferably $N(R^{3'})_2$, $NHCONH_2$ or a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 to 2 N and/or O atoms, which is unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, where $R^{3'}$ is H or A. T is particularly preferably, for example, dimethylamino, diethylamino, morpholin-4-yl, 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl.
T is furthermore preferably a phenyl radical which is monosubstituted by NHCOA, SO_2NH_2 or SO_2A, where A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms.

Ar is preferably unsubstituted phenyl, naphthyl or biphenyl, furthermore preferably phenyl, naphthyl or biphenyl, each of which is monosubstituted, disubstituted or trisubstituted, for example, by A, fluorine, chlorine, bromine, iodine, hydroxyl, methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, nitro, cyano, formyl, acetyl, propionyl, trifluoromethyl, amino, methylamino, ethylamino, dimethylamino, diethylamino, benzyloxy, sulfonamido, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, dimethylsulfonamido, phenylsulfonamido, carboxyl, methoxycarbonyl, ethoxycarbonyl or aminocarbonyl.
Ar is particularly preferably, for example, phenyl which is unsubstituted or monosubstituted or disubstituted by Hal, A, OH or methoxy.
Het is preferably, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-

benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Het can thus, for example, also be 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or -6-yl, 2,3-(2-oxomethylenedioxy)phenyl or alternatively 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het is very particularly preferably a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 to 2 N or O atoms which is unsubstituted or monosubstituted or disubstituted by carbonyl oxygen, such as, for example, morpholin-4-yl, 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-

pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxo-pyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl, 3-oxo-2*H*-pyridazin-2-yl or 2-caprolactam-1-yl.

Het' is preferably, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo-1,4-oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Het' can thus, for example, also be 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo-1,4-oxazinyl,

furthermore preferably 2,3-methylenedioxyphenyl, 3,4-methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)phenyl, 2,3-dihydrobenzofuran-5- or -6-yl, 2,3-(2-oxomethylenedioxy)phenyl or alternatively 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

m is preferably 2, furthermore alternatively 0 or 1.

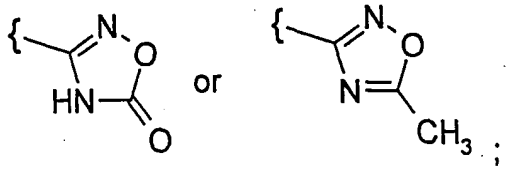
n is preferably 1, furthermore alternatively 0 or 2.

The compounds of the formula I may have one or more chiral centres and therefore occur in various stereoisomeric forms. The formula I covers all these forms.

Accordingly, the invention relates in particular to the compounds of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae Ia to Io, which conform to the formula I and in which the radicals not designated in greater detail are as defined under the formula I, but in which

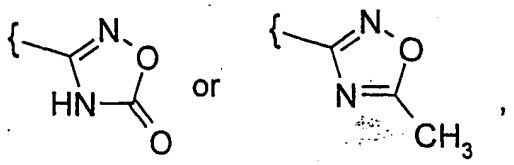
in Ia R^2 is H;

in Ib R^1 is $-C(=NH)-NH_2$ which is unsubstituted or monosubstituted by OH, or



in Ic Ar is phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$;

in Id	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by carbonyl oxygen;
in Ie	W	is NR^3CO;
in If	W	is NR^3CO,
	R^3	is H, A or $-(CH_2)_n$-Ar,
	Ar	is unsubstituted phenyl,
	n	is 0 or 1;
in Ig	X	is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^3$;
in Ih	Y	is Ar-diyl,
	Ar	is unsubstituted phenyl;
in Ii	T	is $N(R^3)_2CON(R^3)_2$, a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by carbonyl oxygen, or phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,
	R^3	is H;
in Ij	R^1	is $-C(=NH)-NH_2$ which is unsubstituted or monosubstituted by OH, or



R^2 is H,

R^3 is H, A or $-(CH_2)_n$-Ar,

W is NR^3CO,

X is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^3$,

Y is Ar-diyl,

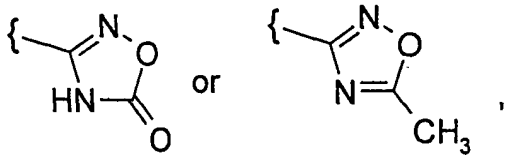
T is $N(R^3)_2CON(R^3)_2$,
a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by carbonyl oxygen or
phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,

Ar is phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

n is 0 or 1;

in Ik R^1 $-C(=NH)-NH_2$ which is unsubstituted or monosubstituted by OH, or



R^2 is H,

R^3 is H, A or $-(CH_2)_n$-Ar,

W is $NR^{3'}CO$,

X is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^{3'}$,

$R^{3'}$ is H,

Y is Ar-diyl,

T is dimethylamino, diethylamino, morpholin-4-yl, 2-oxo-piperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxo-piperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

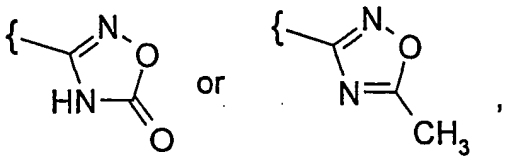
Ar is unsubstituted phenyl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

n is 0 or 1;

in II

R^1 is CN, NH_2, CH_2NH_2, $CH_2CH_2NH_2$, $-C(=NH)-NH_2$ which is unsubstituted or monosubstituted by OH, or



R^2 is H,

R^3 is H, A or $-(CH_2)_n$-Ar,

W is $NR^{3'}CO$,

X is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^{3'}$,

Y is Ar-diyl,

$R^{3'}$ is H,

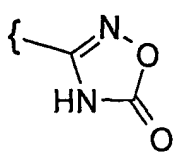
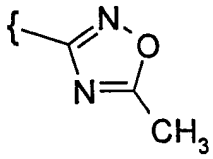
T is dimethylamino, diethylamino, morpholin-4-yl, 2-oxo-piperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxo-piperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

Ar is unsubstituted phenyl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

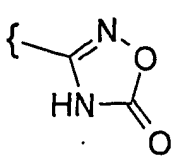
n is 0 or 1;

in Im R^1 is NH_2, CH_2NH_2, $CONH_2$,
-C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or


or

,

R^2 is H,
R^3 is H, A or -$(CH_2)_n$-Ar,
W is $NR^{3'}CO$,
X is -$C(R^3)_2$, -$C(R^3)_2O$- or -$C(R^3)_2NR^{3'}$,
$R^{3'}$ is H,
Y is Ar-diyl,
T is $NHCONH_2$ or
dimethylamino, diethylamino, morpholin-4-yl, 2-oxo-piperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,
Ar is unsubstituted phenyl,
A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,
n is 0 or 1;

in In R^1 is NH_2, CH_2NH_2, $CONH_2$,
-C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or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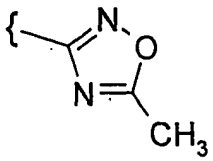

,

R^2 is H,

R^3 is H or phenyl,

W is NHCO,

X is CH_2 or CH(phenyl),

Y is phenylene,

T is $NHCONH_2$ or morpholin-4-yl, 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

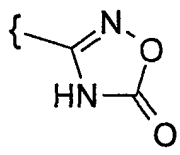
or

phenyl which is monosubstituted by NHCOA, SO_2NH_2 or SO_2A,

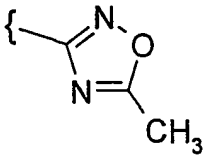
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

in Io R^1 is $CONH_2$ or

-C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or



or



,

R^2 is H,

R^3 is H or phenyl,

W is NHCO,

X is CH_2 or CH(phenyl),

Y is phenylene,

T is $NHCONH_2$ or morpholin-4-yl, 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

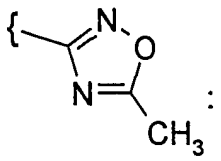
or

phenyl which is monosubstituted by NHCOA, SO_2NH_2 or SO_2A,

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

Preference is furthermore given to the following compounds of the formula I, which, as direct prodrug compounds, can be converted into the corresponding amidino or aminocarbonyl derivatives and

in which R^1 is CN or  :

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(2'-methanesulfonyl-biphenyl-4-oxyl)-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-acetylamino-phenoxy)acetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(2'-methanesulfonyl-biphenyl-4-oxyl)acetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-ureidophenoxy)-acetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-ureidophenoxy)-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxopiperidin-1-yl)phenylamino]acetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxopiperidin-1-yl)phenylamino]-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxo-1*H*-pyridin-1-yl)phenylamino]-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(3-oxomorpholin-4-yl)phenylamino]-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenylamino]-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(3-oxo-2*H*-pyridazin-2-yl)phenylamino]-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-acetamidophenoxy)-2-phenylacetamide,

N-(3-cyanophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,

N-(3-cyanophenyl)-2-(3-acetylaminophenoxy)acetamide,

N-(3-cyanophenyl)-2-(3-ureidophenoxy)acetamide,

N-(3-cyanophenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]acetamide,

N-(3-cyanophenyl)-2-(3-acetylaminophenoxy)-2-phenylacetamide,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

If desired, the starting materials can also be formed in situ so that they are not isolated from the reaction mixture, but instead are immediately converted further into the compounds of the formula I.

Compounds of the formula I can preferably be obtained by liberating compounds of the formula I from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent.

Preferred starting materials for the solvolysis or hydrogenolysis are those which conform to the formula I, but contain corresponding protected amino and/or hydroxyl groups instead of one or more free amino and/or hydroxyl groups, preferably those which carry an amino-protecting group instead of an H atom bonded to an N atom, in particular those which carry an R'-N group, in which R' is an amino-protecting group, instead of an HN group, and/or those which carry a hydroxyl-protecting group instead of the H atom of a hydroxyl group, for example those which conform to the formula I, but carry a -COOR" group, in which R" is a hydroxyl-protecting group, instead of a -COOH group.

Preferred starting materials are also the oxadiazole derivatives, which can be converted into the corresponding amidino compounds.

The amidino group can be liberated from its oxadiazole derivative by, for example, treatment with hydrogen in the presence of a catalyst (for example Raney nickel). Suitable solvents are those indicated below, in particular alcohols, such as methanol or ethanol, organic acids, such as acetic acid or propionic acid, or mixtures thereof. The hydrogenolysis generally carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° (room temperature) and 1-10 bar.

The oxadiazole group is introduced, for example, by reaction of the cyano compounds with hydroxylamine and reaction with phosgene, dialkyl carbonate, chloroformic acid esters, N,N'-carbonyldiimidazole or acetic anhydride.

It is also possible for a plurality of – identical or different – protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protecting groups present are different from one another, they can in many cases be cleaved off selectively.

The term "amino-protecting group" is known in general terms and relates to groups which are suitable for protecting (blocking) an amino group against chemical reactions, but which are easy to remove after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protecting groups are removed after the desired reaction (or reaction sequence), their type and size are furthermore not crucial; however, preference is given to those having 1-20, in particular 1-8, carbon atoms. The term "acyl group" is to be understood in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and, in particular, alkoxy-carbonyl, aryloxycarbonyl and especially aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl and butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl and tolyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butoxycarbonyl) and 2-iodoethoxycarbonyl; aralkoxycarbonyl, such as CBZ ("carbo-benzoxy"), 4-methoxybenzyloxycarbonyl and FMOC; and arylsulfonyl, such as Mtr. Preferred amino-protecting groups are BOC and Mtr, furthermore CBZ, Fmoc, benzyl and acetyl.

The term "hydroxyl-protecting group" is likewise known in general terms and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but are easily removable after the desired chemical reaction has been carried out elsewhere in the molecule. Typical of such groups are the above-mentioned unsubstituted or substituted aryl,

aralkyl or acyl groups, furthermore also alkyl groups. The nature and size of the hydroxyl-protecting groups are not crucial since they are removed again after the desired chemical reaction or reaction sequence; preference is given to groups having 1-20, in particular 1-10, carbon atoms. Examples of hydroxyl-protecting groups are, inter alia, benzyl, 4-methoxybenzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, where benzyl and tert-butyl are particularly preferred.

The compounds of the formula I are liberated from their functional derivatives – depending on the protecting group used – for example using strong acids, advantageously using TFA or perchloric acid, but also using other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but is not always necessary. Suitable inert solvents are preferably organic, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, halogenated hydrocarbons, such as dichloromethane, furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the above-mentioned solvents are furthermore suitable. TFA is preferably used in excess without addition of a further solvent, and perchloric acid is preferably used in the form of a mixture of acetic acid and 70% perchloric acid in the ratio 9:1. The reaction temperatures for the cleavage are advantageously between about 0 and about 50°, preferably between 15 and 30° (room temperature).

The BOC, O-but and Mtr groups can, for example, preferably be cleaved off using TFA in dichloromethane or using approximately 3 to 5N HCl in dioxane at 15-30°, and the FMOC group can be cleaved off using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

Protecting groups which can be removed hydrogenolytically (for example CBZ, benzyl or the liberation of the amidino group from its oxadiazole derivative) can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble-metal catalyst, such as palladium, advantageously on a support, such as carbon). Suitable solvents here are those indicated above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis generally carried out at temperatures between about 0 and 100° and pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group succeeds well, for example, on 5 to 10% Pd/C in methanol or using ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, trifluoromethylbenzene, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said solvents.

A cyano group is converted into an amidino group by reaction with, for example, hydroxylamine followed by reduction of the N-hydroxyamidine using hydrogen in the presence of a catalyst, such as, for example, Pd/C.

In order to prepare an amidine of the formula I, it is also possible to adduct ammonia onto a nitrile. The adduction is preferably carried out in a number of steps by, in a manner known per se, a) converting the nitrile into a thioamide using H_2S, converting the thioamide into the corresponding S-alkylimidothioester using an alkylating agent, for example CH_3I, and reacting the thioester in turn with NH_3 to give the amidine, b) converting the nitrile into the corresponding imidoester using an alcohol, for example ethanol in the presence of HCl, and treating the imidoester with ammonia (Pinner synthesis), or c) reacting the nitrile with lithium bis(trimethylsilyl)amide, and subsequently hydrolysing the product.

Esters can be saponified, for example, using acetic acid or using NaOH or KOH in water, water/THF or water/dioxane, at temperatures between 0 and 100°.

Free amino groups can furthermore be acylated in a conventional manner using an acid chloride or anhydride or alkylated using an unsubstituted or substituted alkyl halide, or reacted with CH_3-C(=NH)-Oet, advantageously in an inert solvent, such as dichloromethane or THF and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

If desired, the starting materials can also be formed in situ so that they are not isolated from the reaction mixture, but instead are immediately converted further into the compounds of the formula I.

Compounds of the formula I in which R^1, R^2 and T are in protected form can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

The reaction is generally carried out in an inert solvent, in the presence of an acid-binding agent, preferably an alkali or alkaline earth metal hydroxide, carbonate or bicarbonate, or in the presence of another salt of a

weak acid of the alkali or alkaline earth metals, preferably of potassium, sodium, calcium or caesium. The addition of an organic base, such as triethylamine, dimethylaniline, pyridine or quinoline, may also be favourable. Depending on the conditions used, the reaction time is between a few minutes and 14 days, and the reaction temperature is between about 0° and 150°, normally between 20° and 130°.

Examples of suitable inert solvents are water; hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters; such as ethyl acetate, or mixtures of the said solvents.

The starting compounds of the formulae II and III are generally known. If they are novel, however, they can be prepared by methods known per se.

In the compounds of the formula III, L is preferably Cl, Br, I or a reactively modified OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy or trifluoromethylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy).

A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, and laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal or alkaline earth metal salts, or into the corresponding ammonium salts using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate).
It is also possible to use physiologically acceptable organic bases, such as, for example, ethanolamine.

Compounds of the formula I according to the invention may be chiral owing to their molecular structure and may accordingly occur in various enantiomeric forms. They can therefore exist in racemic or in optically active form.

Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel). Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/ acetonitrile, for example in the ratio 82:15:3.

The invention furthermore relates to the use of the compounds of the formula I and/or their physiologically acceptable salts for the preparation of a medicament (pharmaceutical preparation), in particular by non-chemical methods. They can be converted here into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or assistant and, if desired, in combination with one or more further active ingredients.

The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios; and, if desired, excipients and/or assistants.

These preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or Vaseline. Suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal administration are suppositories, suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders or also as nasal sprays. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, to prepare injection preparations. The preparations indicated may be sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifying agents, salts for modifying the osmotic pressure, buffer substances, colorants and flavours and/or a plurality of further active ingredients, for example one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for combating and preventing thromboembolic disorders, such as thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexia, angina pectoris, restenosis after angioplasty, claudicatio intermittens, tumours, tumour diseases and/or tumour metastases.

In general, the substances according to the invention are preferably administered in doses between about 1 and 500 mg, in particular between 5 and 100 mg, per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the

efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies. Oral administration is preferred.

The invention furthermore relates to medicaments comprising at least one compound of the formula I and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of a compound of the formula I and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios,
and

(b) an effective amount of a further medicament active ingredient.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules each containing an effective amount of a compound of the formula I and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios,
and an effective amount of a further medicament active ingredient in dissolved or lyophilised form.

The invention furthermore relates to the use of compounds of the formula I and/or their pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios,
for the preparation of a medicament for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexia, angina

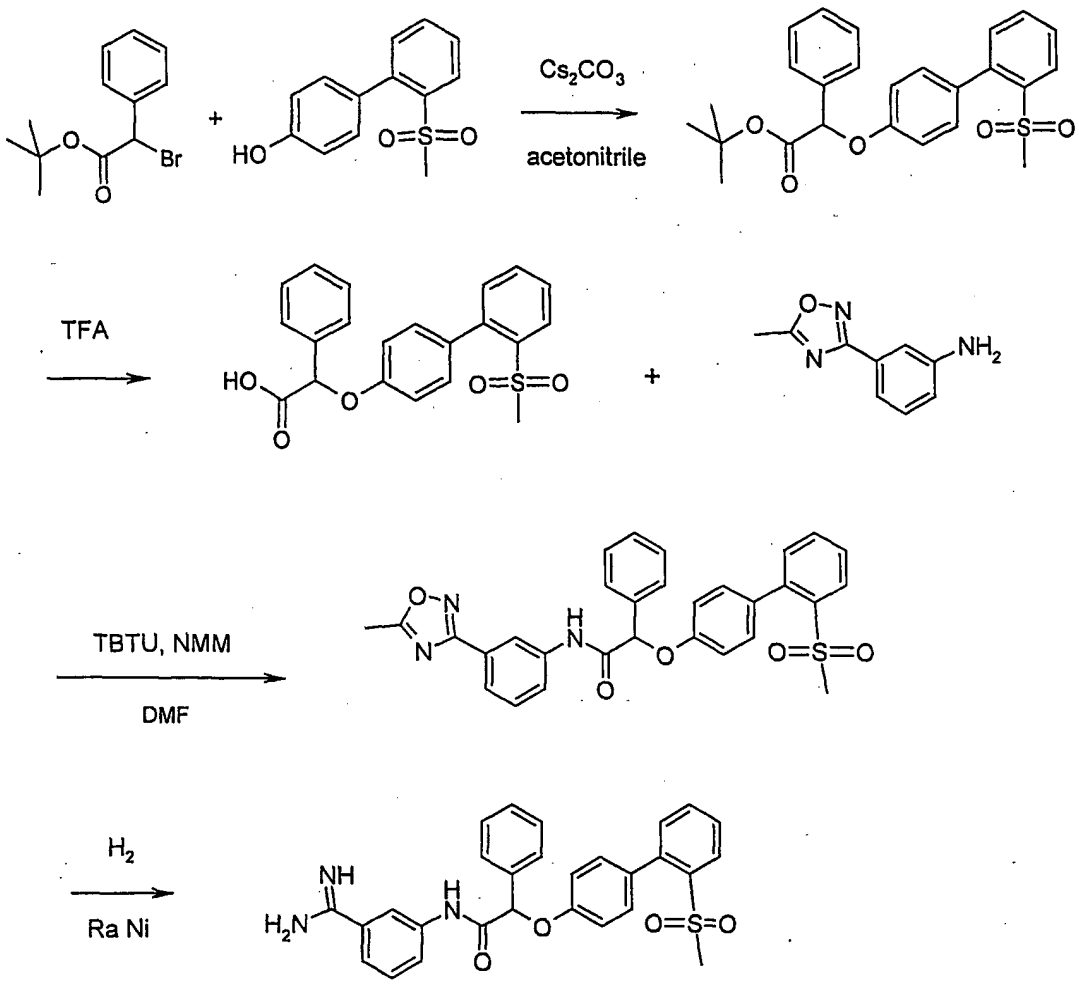
pectoris, restenosis after angioplasty, claudicatio intermittens, tumours, tumour diseases and/or tumour metastases,
in combination with at least one further medicament active ingredient.

Above and below, all temperatures are given in °C. In the following examples, "conventional work-up" means that water is added if necessary, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation. Rf values on silica gel; eluent: ethyl acetate/methanol 9:1.

Mass spectrometry (MS): EI (electron impact ionisation) M^+
FAB (fast atom bombardment) $(M+H)^+$
ESI (electrospray ionisation) $(M+H)^+$
(unless stated otherwise)

Example 1

The preparation of *N*-(3-amidinophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide is carried out as indicated in the following scheme:



1. A solution of 271 mg of tert-butyl (rac)-2-bromo-2-phenylacetate, 248 mg of 2'-methanesulfonylbiphenyl-4-yl alcohol and 358 mg of caesium carbonate in 5 ml of acetonitrile is stirred at room temperature for 26 hours. Conventional work-up gives tert-butyl (rac)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetate as an oil, ESI 365.

2. A solution of 840 mg of tert-butyl (rac)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetate in 8 ml of trifluoroacetic acid is stirred at room temperature for 3 hours. Removal of the solvent gives (rac)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetic acid as an oil, ESI 366.

3. 0.14 ml of 4-methylmorpholine is added to a solution of 120 mg of (rac)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetic acid, 55 mg of 3-(methyl-1,2,4-oxadiazol-3-yl)aniline and O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) in 3 ml of DMF, and the mixture is stirred at room temperature for 20 hours. Conventional work-up gives (rac)-*N*-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide, ESI 540.

4. 200 mg of water-moist Raney nickel and 2 ml of acetic acid are added to a solution of 150 mg of *N*-[3-(5-methyl-1,2,4-oxadiazol-3-yl)-phenyl]-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide in 30 ml of methanol and 2 ml of water, and the mixture s hydrogenated at room temperature and atmospheric pressure for 18 hours. The reaction mixture is filtered, and the residue is evaporated, giving (rac)-*N*-(3-amidinophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide, ESI 500 (M^+).

IC_{50} (Xa) = 1.1×10^{-7} M;
IC_{50} (VIIa) = 4.6×10^{-8} M.

The following compounds are obtained analogously:

N-(3-amidinophenyl)-2-(3-acetylaminophenoxy)acetamide,
N-(3-amidinophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,
N-(3-amidinophenyl)-2-(3-ureidophenoxy)acetamide,
N-(3-amidinophenyl)-2-(3-ureidophenoxy)-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]acetamide,
N-(3-amidinophenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(2-oxopyrrolidin-1-yl)phenylamino]-2-phenylacetamide,

N-(3-amidinophenyl)-2-[4-(2-oxo-1*H*-pyridin-1-yl)phenylamino]-2-phenyl-acetamide,
N-(3-amidinophenyl)-2-[4-(3-oxomorpholin-4-yl)phenylamino]-2-phenyl-acetamide,
N-(3-amidinophenyl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(3-oxo-2*H*-pyridazin-2-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-(3-acetamidophenoxy)-2-phenylacetamide.

Example 2

Analogously to Example 1, 3-cyanoaniline and 2-(2'-methanesulfonyl-biphenyl-4-oxyl)acetic acid give the compound *N*-(3-cyanophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide ("A"), ESI 425 (M^+).

Analogously to Example 1, 3-aminobenzamide and 2-(2'-methanesulfonyl-biphenyl-4-oxyl)acetic acid give the compound *N*-(3-aminocarbonylphenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide, ESI 425 (M^+).

The following compounds are obtained analogously:
N-(3-aminocarbonylphenyl)-2-(3-acetylaminophenoxy)acetamide,
N-(3-aminocarbonylphenyl)-2-(3-ureidophenoxy)acetamide,
N-(3-aminocarbonylphenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]-acetamide,
N-(3-aminocarbonylphenyl)-2-(3-acetylaminophenoxy)-2-phenylacetamide.

Example 3

Reaction of "A" with hydroxylamine hydrochloride and conventional work-up gives
N-[3-(N-hydroxyamidinophenyl)]-2-(2'-methanesulfonylbiphenyl-4-oxyl)-acetamide.

N-[3-(N-hydroxyamidinophenyl)]-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide, ESI 516 (M^+), is obtained analogously.

Example 4

1 ml of methanolic ammonia is added to a solution of 33 mg of *N*-(3-cyano-phenyl)-2-(2'-tert-butylaminosulfonylbiphenyl-4-amino)-2-phenylacetamide in 10 ml of methanol, and the mixture is hydrogenated on Raney nickel. Filtration and purification by chromatography gives 7 mg of *N*-(3-amino-methylphenyl)-2-(2'-tert-butylaminosulfonylbiphenyl-4-amino)-2-phenyl-acetamide, ESI (487).

The following compounds are obtained analogously:

N-(3-aminomethylphenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,
N-(3-aminomethylphenyl)-2-(3-ureidophenoxy)-2-phenylacetamide,
N-(3-aminomethylphenyl)-2-(3-ureidophenoxy)acetamide,
N-(3-aminomethylphenyl)-2-(3-acetylaminophenoxy)-2-phenylacetamide.

Example 5

5.1 3.29 ml of trifluoroacetic anhydride are added dropwise to a suspension of 5 g of *N*-tert-butyl-4'-aminobiphenyl-2-sulfonamide in 70 ml of toluene, and the mixture is stirred at room temperature for a further 48 hours.

Conventional work-up gives *N*-(2'-tert-butylsulfamoylbiphenyl-4-yl)-2,2,2-trifluoroacetamide, ESI 423 ($M+Na^+$).

5.2 2.33 g of caesium carbonate are added to a solution of 2.6 g of *N*-(2'-tert-butylsulfamoylbiphenyl-4-yl)-2,2,2-trifluoroacetamide and 1.1 ml of (rac)-methyl-alpha-bromophenyl acetate in 50 ml of acetonitrile, and the mixture is refluxed for two hours. Conventional work-up gives methyl [(2'-tert-butylsulfamoylbiphenyl-4-yl)(2,2,2-trifluoroethanoyl)amino]phenyl-acetate, ESI 570 ($M+Na^+$).

5.3 15 ml of 1N sodium hydroxide solution are added to a solution of 1.5 g of methyl [(2'-tert-butylsulfamoylbiphenyl-4-yl)(2,2,2-trifluoro-ethanoyl)amino]phenylacetate in 30 ml of methanol, and the mixture is stirred at room temperature for 2 hours. Acidification gives (2'-*tert*-butyl-sulfamoylbiphenyl-4-ylamino)-2-phenylacetic acid, ESI 439 (M^+).

5.4 The preparation of 2-(2'-*tert*-butylsulfamoylbiphenyl-4-ylamino)-*N*-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-phenylacetamide is carried out analogously to Example 1, ESI 596 (M^+).

5.5 The preparation of *N*-(3-amidinophenyl)-2-(2'-tert-butylamino-sulfonylbiphenyl-4-amino)-2-phenylacetamide is carried out analogously to Example 1, ESI 556 (M^+);
IC_{50} (Xa) = 1.4×10^{-7} M;
IC_{50} (VIIa) = 55×10^{-8} M.

5.6 1 ml of anisole is added to a solution of 0.7 g of *N*-(3-amidino-phenyl)-2-(2'-tert-butylaminosulfonylbiphenyl-4-amino)-2-phenylacetamide in 10 ml of trifluoroacetic acid, and the mixture is stirred at room temperature for 24 hours, giving *N*-(3-amidinophenyl)-2-(2'-aminosulfonyl-biphenyl-4-amino)-2-phenylacetamide, trifluoroacetate, ESI 500;

IC_{50} (Xa) = 2.0×10^{-8} M;

IC_{50} (VIIa) = 1.3×10^{-8} M.

The examples below relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 g of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is

pressed in a conventional manner to give tablets in such a way that each tablet contains 10 mg of active ingredient.

Example F: Coated tablets

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

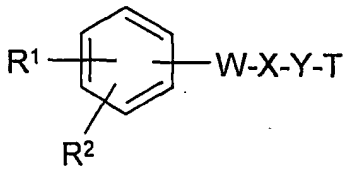
2 kg of active ingredient of the formula I are introduced in a conventional manner into hard gelatine capsules in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Patent claims

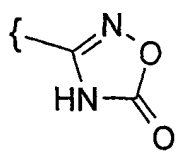
1. Compounds of the formula I



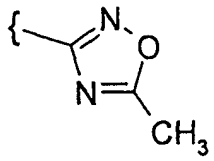
I

in which

R^1 is CN, or -C(=NH)-NH_2, $CON(R^3)_2$ or -$[C(R^4)_2]_nN(R^3)_2$, each of which is unsubstituted or monosubstituted by $C(=O)R^3$, $COOR^3$, OR^3 or by a conventional amino-protecting group, or



or



,

R^2 is H, Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, -[C(R4)2]n-Ar, -[C(R4)2]n-Het or -[C(R4)2]n-cycloalkyl,

R^3 is H, A, -$[C(R^4)_2]_n$-Ar, -$[C(R^4)_2]_n$-Het or -$[C(R^4)_2]_n$-cycloalkyl,

R^4 is H or A,

W is -NR^3CO-, -$NR^3COC(R^4)_2$, $NR^3C(R^4)_2$ or -$C(R^4)_2NR^3C(R^4)_2$-,

X is -$C(R^3)_2$-, -$[C(R^3)_2]_2$-, -$C(R^3)_2O$- or -$C(R^3)_2NR^3$,

Y is alkylene, cycloalkylene, Het-diyl or Ar-diyl,

T is OR^3, $N(R^3)_2$, $N(R^3)_2CON(R^3)_2$,

a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, -$[C(R^4)_2]_n$-Ar, -$[C(R^4)_2]_n$-Het, -$[C(R^4)_2]_n$-cycloalkyl, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, $S(O)_mA$

and/or carbonyl oxygen, or

a phenyl radical which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, -$[C(R^4)_2]_n$-Ar, -$[C(R^4)_2]_n$-Het, -$[C(R^4)_2]_n$-cycloalkyl, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3 or $S(O)_mA$,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by -CH=CH- groups and/or, in addition, 1-7 H atoms may be replaced by F,

Ar is phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^4, $N(R^4)_2$, $NR^4CON(R^4)_2$, NO_2, CN, $COOR^4$, $CON(R^4)_2$, NR^4COA, NR^4SO_2A, COR^4, SO_2NR^4 or $S(O)_mA$,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, -$[C(R^4)_2]_n$-Ar, -$[C(R^4)_2]_n$-Het', -$[C(R^4)_2]_n$-cycloalkyl, OR^3, $N(R^3)_2$, $NR^4CON(R^4)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, $S(O)_mA$ and/or carbonyl oxygen,

Het' is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms which is unsubstituted or monosubstituted or disubstituted by Hal, A, OR^3, $N(R^3)_2$, NO_2, CN, $COOR^3$, $CON(R^3)_2$, NR^3COA, NR^3SO_2A, COR^3, SO_2NR^3, $S(O)_mA$ and/or carbonyl oxygen,

Hal is F, Cl, Br or I,

m and n are each, independently of one another, 0, 1 or 2,

and their pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios.

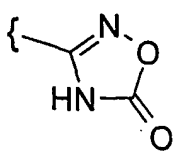
2. Compounds according to Claim 1, in which

R^2 is H,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

3. Compounds according to Claim 1 or 2, in which

R^1 is -C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or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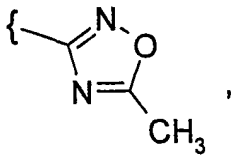

,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

4. Compounds according to Claim 1, 2 or 3, in which

Ar is phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

5. Compounds according to Claims 1-4, in which

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by carbonyl oxygen,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

6. Compounds according to Claims 1-5, in which

W is NR^3CO,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

7. Compounds according to Claims 1-6, in which

W is NR^3CO,

R^3 is H, A or $-(CH_2)_n$-Ar,

Ar is unsubstituted phenyl,

n is 0 or 1,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

8. Compounds according to Claims 1-7, in which

X is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^3$,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

9. Compounds according to Claims 1-8, in which

Y is Ar-diyl,

Ar is unsubstituted phenyl,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

10. Compounds according to Claims 1-9, in which

T is $N(R^3)_2CON(R^3)_2$,

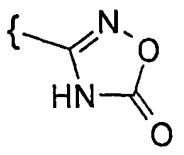
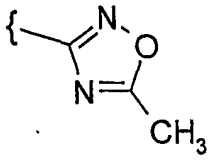
a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by carbonyl oxygen or phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,

R^3 is H,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

11. Compounds according to Claim 1, in which

R^1 is -C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or


or

,

R^2 is H,

R^3 is H, A or -$(CH_2)_n$-Ar,

W is NR^3CO,

X is -$C(R^3)_2$, -$C(R^3)_2O$- or -$C(R^3)_2NR^3$,

Y is Ar-diyl,

T is $N(R^3)_2CON(R^3)_2$,

a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1 or 2 N and/or O atoms which is monosubstituted or disubstituted by carbonyl oxygen or phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,

Ar is phenyl which is unsubstituted or monosubstituted or disubstituted by SO_2NH_2, SO_2A or $NHCONH_2$,

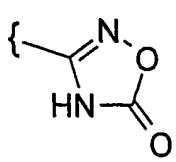
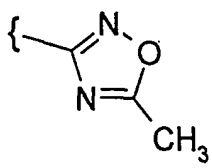
A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

n is 0 or 1,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

12. Compounds according to Claim 1, in which

R^1 is -C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or


or

,

R^2 is H,

R^3 is H, A or $-(CH_2)_n$-Ar,

W is $NR^{3'}CO$,

X is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^{3'}$,

$R^{3'}$ is H,

Y is Ar-diyl,

T is dimethylamino, diethylamino, morpholin-4-yl, 2-oxo-piperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

Ar is unsubstituted phenyl,

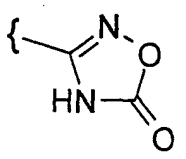
A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

n is 0 or 1,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

13. Compounds according to Claim 1, in which

R^1 is CN, NH_2, CH_2NH_2, $CH_2CH_2NH_2$, $-C(=NH)-NH_2$ which is unsubstituted or monosubstituted by OH, or



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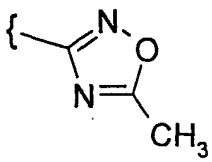


,

R^2 is H,

R^3 is H, A or $-(CH_2)_n$-Ar,

W is $NR^{3'}CO$,

X is $-C(R^3)_2$, $-C(R^3)_2O-$ or $-C(R^3)_2NR^{3'}$,

Y is Ar-diyl,

$R^{3'}$ is H,

T is dimethylamino, diethylamino, morpholin-4-yl, 2-oxo-piperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidine-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

Ar is unsubstituted phenyl,

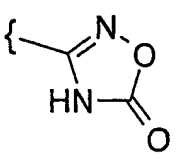
A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

n is 0 or 1,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

14. Compounds according to Claim 1, in which

R^1 is NH_2, CH_2NH_2, $CONH_2$,
-C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or



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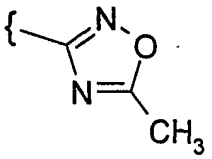


,

R^2 is H,

R^3 is H, A or -$(CH_2)_n$-Ar,

W is $NR^{3'}CO$,

X is -$C(R^3)_2$, -$C(R^3)_2O$- or -$C(R^3)_2NR^{3'}$,

$R^{3'}$ is H,

Y is Ar-diyl,

T is $NHCONH_2$ or
dimethylamino, diethylamino, morpholin-4-yl, 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxo-morpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidine-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

Ar is unsubstituted phenyl,

A is unbranched or branched alkyl having 1-6 carbon atoms, in which 1-7 H atoms may be replaced by F,

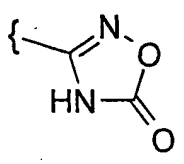
n is 0 or 1,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

15. Compounds according to Claim 1, in which

R^1 is NH_2, CH_2NH_2, $CONH_2$,

-C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or



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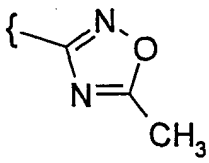


,

R^2 is H,

R^3 is H or phenyl,

W is NHCO,

X is CH_2 or CH(phenyl),

Y is phenylene,

T is $NHCONH_2$ or morpholin-4-yl, 2-oxopiperidin-1-yl, 2-oxo-pyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxopyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

or

phenyl which is monosubstituted by NHCOA, SO_2NH_2 or SO_2A,

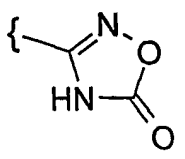
A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

16. Compounds according to Claim 1, in which

R^1 is $CONH_2$, or

-C(=NH)-NH_2 which is unsubstituted or monosubstituted by OH, or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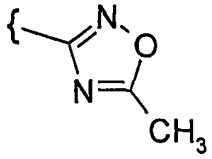

,

R^2 is H,

R^3 is H or phenyl,

W is NHCO,

X is CH_2 or CH(phenyl),

Y is phenylene,

T is $NHCONH_2$ or 2-oxopiperidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-1*H*-pyridin-1-yl, 3-oxomorpholin-4-yl, 4-oxo-1*H*-pyridin-1-yl, 2,6-dioxopiperidin-1-yl, 2-oxopiperazin-1-yl, 2,5-dioxo-pyrrolidin-1-yl, 2-oxo-1,3-oxazolidin-3-yl or 3-oxo-2*H*-pyridazin-2-yl,

or

phenyl which is monosubstituted by NHCOA, SO_2NH_2 or SO_2A,

A is alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

17. Compounds according to Claim 1, selected from the group consisting of

N-(3-amidinophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide,

N-(3-amidinophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,

N-(3-amidinophenyl)-2-(3-ureidophenoxy)acetamide,
N-(3-amidinophenyl)-2-(3-ureidophenoxy)-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]acetamide,
N-(3-amidinophenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(2-oxopyrrolidin-1-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(2-oxo-1*H*-pyridin-1-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(3-oxomorpholin-4-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenylamino]-2-phenylacetamide,
N-(3-amidinophenyl)-2-[4-(3-oxo-2*H*-pyridazin-2-yl)phenylamino]-2-phenylacetamide,
N-(3-cyanophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,
N-(3-aminocarbonylphenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-acetamide,
N-(3-aminocarbonylphenyl)-2-(3-ureidophenoxy)acetamide,
N-(3-aminocarbonylphenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]-acetamide,
N-[3-(N-hydroxyamidinophenyl)]-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,
N-[3-(N-hydroxyamidinophenyl)]-2-(2'-methanesulfonylbiphenyl-4-oxyl)-2-phenylacetamide,
N-(3-aminomethylphenyl)-2-(2'-tert-butylaminosulfonylbiphenyl-4-amino)-2-phenylacetamide,
N-(3-aminomethylphenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)-acetamide,
N-(3-aminomethylphenyl)-2-(3-ureidophenoxy)-2-phenylacetamide,

N-(3-aminomethylphenyl)-2-(3-ureidophenoxy)acetamide,
2-(2'-tert-butylsulfamoylbiphenyl-4-ylamino)-*N*-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-phenylacetamide,
N-(3-amidinophenyl)-2-(2'-tert-butylaminosulfonylbiphenyl-4-amino)-2-phenylacetamide,
N-(3-amidinophenyl)-2-(2'-aminosulfonylbiphenyl-4-amino)-2-phenylacetamide,
N-(3-amidinophenyl)-2-(3-acetylaminophenoxy)acetamide,
N-(3-aminocarbonylphenyl)-2-(3-acetylaminophenoxy)acetamide,
and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

18. Compounds according to Claim 1, selected from the group consisting of

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(2'-methanesulfonyl-biphenyl-4-oxyl)-2-phenylacetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-acetylamino-phenoxy)acetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(2'-methanesulfonyl-biphenyl-4-oxyl)acetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-ureidophenoxy)-acetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-ureidophenoxy)-2-phenylacetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxopiperidin-1-yl)phenylamino]acetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxopiperidin-1-yl)phenylamino]-2-phenylacetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxo-1*H*-pyridin-1-yl)phenylamino]-2-phenylacetamide,

N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(3-oxomorpholin-4-yl)phenylamino]-2-phenylacetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(2-oxo-1,3-oxazolidin-3-yl)phenylamino]-2-phenylacetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-[4-(3-oxo-2*H*-pyridazin-2-yl)phenylamino]-2-phenylacetamide,
N-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-2-(3-acetamidophenoxy)-2-phenylacetamide,
N-(3-cyanophenyl)-2-(2'-methanesulfonylbiphenyl-4-oxyl)acetamide,
N-(3-cyanophenyl)-2-(3-acetylaminophenoxy)acetamide,
N-(3-cyanophenyl)-2-(3-ureidophenoxy)acetamide,
N-(3-cyanophenyl)-2-[4-(2-oxopiperidin-1-yl)phenylamino]acetamide,
N-(3-cyanophenyl)-2-(3-acetylaminophenoxy)-2-phenylacetamide,

and pharmaceutically usable derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios.

19. Process for the preparation of compounds of the formula I according to Claims 1-18 and their pharmaceutically tolerated salts and solvates, characterised in that

a) they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent by

i) liberating an amidino group from their hydroxyl, oxadiazole or oxazolidinone derivative by hydrogenolysis or solvolysis,

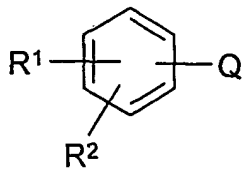
ii) replacing a conventional amino-protecting group by hydrogen by treatment with a solvolysing or hydrogenolysing agent, or liberating an amino group protected by a conventional protecting group,

or

b) a cyano group is converted into an N-hydroxyamidino group ,

or

c) a compound of the formula II

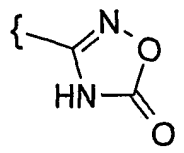


II

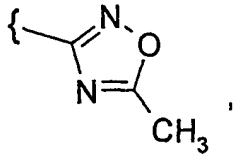
in which

Q is HNR^3- or $C(R^4)_2NHR^3$,

R^1 is $-C(=NH)-NH_2$ which is monosubstituted by $C(=O)R^3$, $COOR^3$, OR^3 or by a conventional amino-protecting group, or



or



,

and R^2, R^3 and R^4 are as defined in Claim 1, with the proviso that, if R^2 contains a free amino group, this in protected form,

is reacted with a compound of the formula III

III

Z-X-Y-T III

in which

Z is -CO-L, -C(R^4)$_2$-CO-L or -C(R^4)$_2$-L,

L is Cl, Br, I or a free or reactively functionally modified OH group, and

X, Y and T are as defined in Claim 1, with the proviso that, if T is or contains a free amino group, this in protected form,

and/or

d) a base or acid of the formula I is converted into one of its salts.

20. Compounds of the formula I according to one or more of Claims 1 to 18 as inhibitors of coagulation factor Xa.

21. Compounds of the formula I according to one or more of Claims 1 to 18 as inhibitors of coagulation factor VIIa.

22. Medicament comprising at least one compound of the formula I according to one or more of Claims 1 to 18 and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios, and, if desired, excipients and/or assistants.

23. Medicament comprising at least one compound of the formula I according to one or more of Claims 1 to 18 and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios, and at least one further medicament active ingredient.

24. Use of compounds according to one or more of Claims 1 to 18 and/or their physiologically acceptable salts and solvates for the preparation of a medicament for the treatment of thrombosis, myocardial infarc-

tion, arteriosclerosis, inflammation, apoplexia, angina pectoris, restenosis after angioplasty, claudicatio intermittens, tumours, tumour diseases and/or tumour metastases.

25. Set (kit) consisting of separate packs of

(a) an effective amount of a compound of the formula I according to one or more of Claims 1 to 18 and/or its pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios,

and

(b) an effective amount of a further medicament active ingredient.

26. Use of compounds of the formula I according to one or more of Claims 1 to 18 and/or their pharmaceutically usable derivatives, solvates and stereoisomers, including mixtures thereof in all ratios, for the preparation of a medicament for the treatment of thrombosis, myocardial infarction, arteriosclerosis, inflammation, apoplexia, angina pectoris, restenosis after angioplasty, claudicatio intermittens, tumours, tumour diseases and/or tumour metastases, in combination with at least one further medicament active ingredient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/01114

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C317/22 C07C275/34 C07D211/76 C07D207/27 C07D213/64
C07D265/28 C07D233/36 C07C257/18 C07C237/42 C07D271/06
C07D413/12 C07C255/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 09093 A (ZHAO ZUCHUN ;BERLEX LAB (US); SAKATA STEVEN T (US); SHAW KENNETH J) 8 February 2001 (2001-02-08) page 11, line 1 - line 21; claims ---	1-26
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A	page 4, line 40 -page 8, line 35 --- -/--	1-26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 June 2002	09/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seufert, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/01114

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LEE, SO HA ET AL: "Synthesis and antifungal activities of N-aryl-4-phenyl-3-(4-phenoxyphenyl)butanamides" retrieved from STN Database accession no. 132:22731 CA XP002203316 abstract & ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) (1999), 332(10), 333-336 , 1999,	1,2,6-9
X	DE 29 26 049 A (BASF A.-G., FED. REP. GER.) 8 January 1981 (1981-01-08) page 24, line 1 -page 27, line 15 table pages 28-31	1,2,4-9
X	US 2 361 327 A (SPARKS CHILES E) 24 October 1944 (1944-10-24) column 2, line 14 - line 44 examples IV, VI-XI, XVII, XVIII	1,2,6-9
A	EP 0 976 722 A (AJINOMOTO KK) 2 February 2000 (2000-02-02) page 3, line 1 - line 31; claims; examples	1-26
A	WO 00 71508 A (COR THERAPEUTICS INC) 30 November 2000 (2000-11-30) cited in the application page 1, line 8 - line 17; claims; examples	1-26
P,X	DATABASE CHEMCATS 'Online! Database accession no. 2002:1238851 XP002203317 abstract & Ambinter: Exploratory Library, 21-01-02	1,2,6-9
P,X	WO 02 08177 A (DORSCH DIETER ;GLEITZ JOHANNES (DE); JURASZYK HORST (DE); MEDERSKI) 31 January 2002 (2002-01-31) page 4, line 14 - line 25; claims 1,13-19	1-5, 8-10, 19-26

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, with regard to the examples and the subject-matter considered to be supported (Art. 6 PCT) the search has been restricted to compounds of formula I, whereby
R1 is CN, C(=NH)-NH2 (optionally being substitued by a hydroxy group), CONH2, (CH2)nNH2 with n=0,1 and the two specific oxadiazols groups mentioned in claim 1;
R2=H;
W=NR3CO with R3 as defined in claim 1
X='C(R3)2!2, C(R3)2O, C(R3)2NR3 with R3 as defined in claim 1
Y=Ar-diyl
T as defined in claim 1 and
R1 is in meta position to the group W-X-Y-T

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/01114

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/01114

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